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Full paper

Dentin hypersensitivity-like tooth pain seen in patients receiving steroid therapy: An exploratory study

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ABSTRACT

To ascertain whether steroid therapy evokes dentin hypersensitivity (DH)-like tooth pain, we performed a study based on compelling evidence from patients receiving steroid therapy. An exploratory study was conducted using a questionnaire for 220 patients prescribed steroids who attended the Department of Hematology and Rheumatology of Tohoku University Hospital. Group comparisons between patients with and without steroid pulse therapy were analysed by statistical means. In this study, any DH-like tooth pain that commenced subsequent to steroid treatment was defined as steroid-derived (SD) tooth pain. The prevalence of SD tooth pain was 17.7% (39/220 patients). SD tooth pain was triggered in many vital teeth by cold and/or hot water (84.2% and 23.7%, respectively) with the pain characterised as continuous, in contrast to typical DH tooth pain. SD tooth pain was significantly more frequent in pulse therapy patients than in non-pulse therapy patients ($p < 0.05$). Logistic regression analysis adjusted for age and sex showed similar results (odds ratio = 3.74, $p = 0.013$). Moreover, a positive correlation was observed between the steroid dose and pain score ($\rho = 0.642$). Dose reduction or discontinuation of steroid therapy relieved SD tooth pain in all cases. Thus, steroid therapy can evoke DH-like tooth pain during treatment.

1. Introduction

Dentin hypersensitivity (DH) is a common oral condition characterised by intense, transient pain induced by stimulation or irritation of exposed dentin, and is generally elicited in response to chemical, cold, tactile, or osmotic stimuli (1). Numerous informal reports on social media (e.g., weblogs, Twitter, and Facebook) have revealed the prevalence of severe DH-like tooth pain in patients taking steroids. Several of these reports have stated that this pain is among the most irritating of steroid-derived side effects, along with having a puffy face caused by water retention. However, DH-like tooth pain is not documented in the academic literature as one of the side effects of steroid therapy, although steroids have many well-known side effects (e.g., lipodystrophy, neuropsychiatric disorders, skin disorders, muscle cramps, and weakness in proximal muscles) (2).

Paradoxically, therapies involving corticosteroids are well known to relieve pain because of their anti-inflammatory and/or anti-oedema effects (3). However, it is unknown whether steroid administration can influence the pain threshold. We recently found that, using a rat model, prednisolone induces microglial activation specifically in the subnucleus caudalis, and not in other nuclei of the trigeminal sensory complex (4), where the primary sensory nerves innervating the pulp project. This finding suggests that steroid therapy may be associated with DH-like tooth pain in patients.

Here, we surveyed patients undergoing steroid therapy in an exploratory study. We used a questionnaire that included items exploring sex, age, primary disease, steroid dose, experience of DH-like tooth pain, and pain characteristics (e.g., triggers and severity)

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to determine the potential relationship between steroid therapy and DH-like tooth pain.

2. Materials and methods

2.1. Study population

The subjects comprised 220 patients (40 males and 180 females) with a mean age of 49.9 years (range: 17–87 years) who attended and received steroid therapy at the Department of Hematology and Rheumatology of Tohoku University Hospital. In this study, a control group of non-steroid subjects was not included because our preliminary survey showed all non-steroid subjects who met the inclusion and exclusion criteria described below did not suffer from DH-like tooth pain. The most common primary diseases for which patients were prescribed steroid therapy were systemic lupus erythematosus (SLE; n = 93), rheumatoid arthritis (RA; n = 70), Sjögren's syndrome (n = 17), Takayasu's arteritis (n = 16), mixed connective tissue disease (n = 9), and dermatomyositis (n = 5). Patients who experienced tooth pain before steroid therapy, dental caries (including wedge-shaped defects), and/or had five or fewer remaining vital teeth were excluded from the study after clinical examination (dental checkup) at the Department of Oral Diagnosis of Tohoku University Hospital. The present study was approved by the Ethics Committee of Tohoku University Graduate School of Dentistry (approval no. 2011/22-31). Written informed consent was obtained from all participants or their guardians (17–19-year-old participants). This survey was conducted following the ethical principles of medical investigation involving human subjects under the Helsinki Declaration of the World Medical Association (http://www.wma.net).

2.2. Study design

An exploratory study using a questionnaire was carried out at Tohoku University Hospital between June 2011 and July 2015. The questionnaire was administered once and patients were asked questions on items such as sex, age, primary disease, treatment received (e.g., steroid therapy and/or steroid pulse therapy), experience of DH-like tooth pain, and pain characteristics (e.g., site, onset, triggers, and the pain severity score expressed on a visual analogue scale [VAS]). Steroid pulse therapy comprised methylprednisolone administration (500–1000 mg/day, i.v.) for 3 days. Non-pulse therapy consisted of prednisolone administration (1–200 mg/day, p.o.). We compared the maximum pain sensation (VAS based on patient recall) with the present maximum pain sensation (VAS described at that time). Steroid doses at these time points were determined using the patients' medical charts. Changes in the pain score were compared before and after reduction or discontinuation of the steroid. For the purposes of this study, any DH-like tooth pain that commenced subsequent to taking steroids was defined as 'steroid-derived (SD) tooth pain' after a dental checkup according to the inclusion and exclusion criteria described above. We also examined the effects of dental treatments generally provided for DH, which were delivered upon patient request for alleviation of SD tooth pain. These DH treatments included application of MS Coat ONE (Sun Medical Co., Ltd., Moriyama, Japan), Teethmate Desensitizer (Kuraray Noritake Dental Inc., Tokyo, Japan), and Saforide (Bee Brand Medico Dental Co., Ltd., Osaka, Japan).

2.3. Statistical analysis

The chi-squared test was used for comparison of qualitative data. Fisher's exact test was used for comparison of steroid pulse therapy and presence of tooth pain because of the small expected value. Logistic regression analysis was then applied to estimate the odds ratio (OR) of steroid pulse therapy for presence of tooth pain adjusting for age and sex. To consider the effect of diseases on tooth pain, the presence of SLE, RA, and other diseases was added to the model.

The relationship between steroid dose and pain sensation evaluated by the VAS was analysed by calculating the correlation coefficient (ρ). Significant differences in tooth pain as quantified by the VAS at the maximum steroid dose and after discontinuation or dose reduction were determined using the paired t-test. Statistical analyses were performed using PASW statistics, v18.0 (SPSS Inc., Chicago, IL, USA). Logistic regression analyses were conducted using STATA SE version 14.1 (Stata Corp, College Station, TX, USA). Differences were considered significant at $p < 0.05$.

3. Results

3.1. Prevalence of SD tooth pain in patients receiving pulsed and non-pulsed steroid therapy

As shown in Table 1, the prevalence of SD tooth pain in patients taking steroids was 17.7% (39/220 patients). There were no significant differences in the prevalence between sex ($p = 0.7135$) or amongst patients with SLE (n = 93), RA (n = 70), or other diseases (n = 97) as the primary disease ($p = 0.4374$). Thirty-six patients had more than one primary disease. The prevalence of SD tooth pain was significantly more frequent in patients treated with steroid pulse therapy (41.2%; 7/17 patients) than in those receiving non-pulse therapy (15.8%; 32/203 patients; $p < 0.05$) (Fig. 1).

Table 2 shows the results of logistic regression analysis. After adjusting for age and sex, logistic regression analysis showed that steroid pulse therapy was significantly associated with SD tooth pain (OR = 3.74, $p = 0.013$). Steroid pulse therapy remained significantly associated with SD tooth pain after considering the effects of diseases (OR = 3.34, $p = 0.029$), indicating that the effect of diseases on SD tooth pain was small.

3.2. Relationship between prednisolone dose and pain severity and the effect of steroid discontinuation or dose reduction on SD tooth pain

A positive correlation between steroid dose (prednisolone) and pain score was observed ($\rho = 0.642$) (Fig. 2). The highest pain score

Table 1
Distribution of patients with steroid treatment (n = 220).

Variables		N (%)
Pain	(−)	181 (82.27)
	(+)	39 (17.73)
Pulse	(−)	203 (92.27)
	(+)	17 (7.73)
Age	40>	69 (31.36)
	40–59	79 (35.91)
	59<	72 (32.73)
Sex	Men	40 (18.18)
	Women	180 (81.82)
SLE	(−)	127 (57.73)
	(+)	93 (42.27)
RA	(−)	150 (68.18)
	(+)	70 (31.82)
Other diseases	(−)	121 (55.00)
	(+)	99 (45.00)

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; 'Other diseases' include Sjögren's syndrome, Takayasu's arteritis, mixed connective-tissue disease, and dermatomyositis.

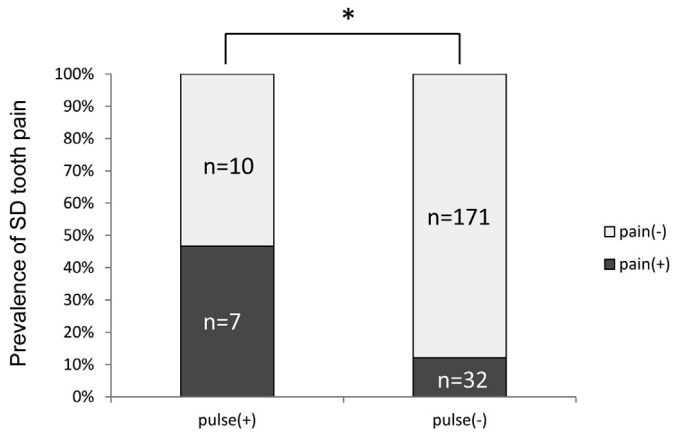

Fig. 1. Prevalence of steroid-induced tooth pain in patients receiving pulsed and non-pulsed steroid therapy. Responses to a questionnaire exploring the development of tooth pain following steroid administration. Patients were subdivided by the type of therapy received and asked whether they experienced tooth pain subsequent to starting therapy. Differences between the groups were statistically analysed using the chi-squared test, with $p < 0.05$ (*) considered to be significant.

expressed on the VAS was observed when the maximum dose of steroid was administered and then decreased concomitant with dose reduction or discontinuation of the steroid in all cases (Fig. 3). Mean differences in pain scores before and after reduction or discontinuation of the steroid were −41.36 ($p < 0.001$) for all cases, −43.20 ($p < 0.001$) for reduction, and −35.76 ($p = 0.0057$) for discontinuation. After reduction or discontinuation of the steroid, 66.7% of patients with pain (26/39) sufficiently recovered to record a zero pain score, with the remainder reporting decreased (but continuous) pain. Specifically, all patients who discontinued steroid therapy achieved zero pain (7/7; 100%). Of the remaining 32 patients who only received dose reduction, a zero pain score was achieved in 19 patients, with pain remaining in 40.6% (13/32) of patients.

3.3. Features of SD tooth pain

Fig. 4A shows the frequency of different triggers of SD tooth pain. Approximately 84% of patients felt pain when drinking cold water and approximately 24% felt pain even when drinking hot water. The pain simultaneously occurred in several vital teeth in all cases (data not shown). In particular, SD tooth pain was evoked even in teeth without obvious root exposure. It was characterised as continuous pain (97.4%; 38/39 patients), in contrast to the transient pain generally associated with 'true' DH tooth pain. Fig. 4B shows the degree of SD tooth pain, with approximately 64% of patients finding it 'tolerable', although 31% found the symptoms to be 'intolerable'. Almost all patients expressed that the pain made them feel 'anxious (intolerable and tolerable)' (Fig. 4B).

3.4. Effects of dental treatments generally provided for DH

Dental treatment to address SD tooth pain was provided to 15 of the 39 patients with pain, at their request. This treatment decreased tooth pain but was only temporarily effective, lasting 1–7 days before the pain returned to pre-treatment levels.

4. Discussion

Adrenocorticosteroid, a glucocorticoid hormone produced by the adrenal cortex, is widely applied for the treatment of various diseases because of its strong anti-inflammatory and immunoregulatory effects (5–7). However, it has not been shown to induce pain or increase pain sensations in any organ. In the present study, we demonstrated that patients receiving steroid therapy frequently experienced severe tooth pain during medication, which we defined as 'steroid-derived (SD) tooth pain'. This pain was more frequently observed in patients receiving steroid pulse therapy than patients receiving non-pulse therapy ($p < 0.05$; Fig. 1). Logistic regression analysis also showed that steroid pulse therapy was significantly associated with SD tooth pain after adjusting for age and sex (OR = 3.74, $p = 0.013$; Table 2) and the effects of diseases (OR = 3.34, $p = 0.029$; Table 2). Additionally, there was a positive correlation between the dose of prednisolone and pain sensation (Fig. 2), and pain was reduced upon reduction of steroid dose and completely disappeared after discontinuation of steroid therapy (Fig. 3). These findings suggest a potential relationship between steroid therapy and induced tooth pain (SD tooth pain). Symptoms of SD tooth pain imitate DH, which is a common global oral symptom associated with exposed dentinal surfaces. This symptom may lead dentists to misdiagnosis patients for pain control. Here, we characterised the differences between SD tooth pain and true DH pain as follows: (i) the pain was not transient, but continuous and severe; (ii) the pain was triggered by both cold and hot water (Fig. 4A); (iii) the pain occurred not only in one tooth, but in multiple vital teeth simultaneously; (iv) the pain was evoked even in teeth without obvious root exposure; (v) standard DH treatment was effective at only temporarily reducing pain; and (vi) the pain

Table 2
Results of logistic regression analysis for tooth pain (n = 220).

		Age and sex adjusted		Multivariate adjusted	
		Odds ratio (95% confidence interval)	*p*-Value	Odds ratio (95% confidence interval)	*p*-Value
Pulse	(−)	1.00		1.00	
	(+)	3.74 (1.33–10.55)	0.013	3.34 (1.13–9.87)	0.029
Age	40<	1.00		1.00	
	40–59	0.91 (0.40–2.07)	0.816	0.93 (0.41–2.15)	0.871
	59<	0.47 (0.18–1.20)	0.114	0.48 (0.18–1.27)	0.138
Sex	Men	1.00		1.00	
	Women	1.19 (0.45–3.13)	0.73	1.22 (0.45–3.28)	0.696
SLE	(−)	–		1.00	
	(+)	–		0.85 (0.26–2.71)	0.778
RA	(−)	–		1.00	
	(+)	–		0.68 (0.25–1.86)	0.453
Other diseases	(−)	–		1.00	
	(+)	–		0.96 (0.31–2.99)	0.944

SLE, systemic lupus erythematosus; RA, rheumatoid arthritis; 'Others' includes Sjögren's syndrome, Takayasu's arteritis, mixed connective-tissue disease, and dermatomyositis.

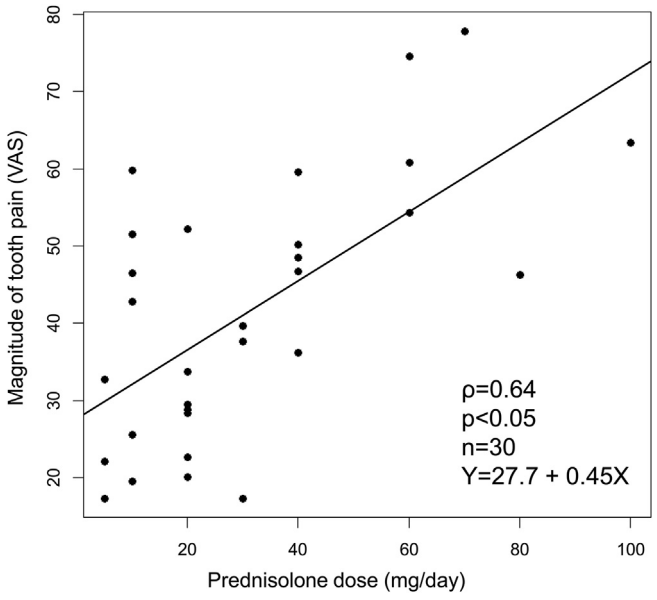

Fig. 2. Relationship between prednisolone dose and pain severity. The magnitude of tooth pain was quantified using a visual analogue scale (VAS) and plotted against the prednisolone dose. A correlation analysis was performed to determine the relationship between these parameters.

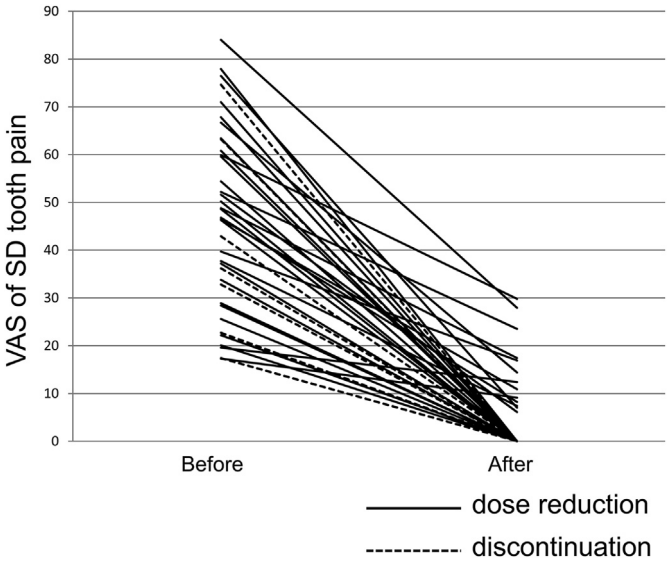

Fig. 3. Effect of steroid discontinuation or dose reduction on steroid-derived tooth pain. Magnitude of steroid-induced tooth pain at the maximum steroid dose and after discontinuation or dose reduction of the steroid was quantified on the same VAS used in Fig. 2. Lines indicate the direction of change in pain severity after dose reduction (solid lines) or complete discontinuation (dotted lines). Mean differences in pain scores before and after reduction or discontinuation of the steroid were −41.36 ($p < 0.001$) for all cases, −43.20 ($p < 0.001$) for reduction, and −35.76 ($p = 0.0057$) for discontinuation (paired t-test).

diminished or resolved with reduction or discontinuation of the steroid. Table 3 summarises the differences in the manifestations of SD tooth pain and true DH pain. Interestingly, our preliminary survey showed all non-steroid subjects who met the study inclusion and exclusion criteria did not suffer from DH-like tooth pain characterised by the manifestations above (data not shown).

To our knowledge, this is the first report to demonstrate a close causal relationship between steroid therapy and tooth pain that is

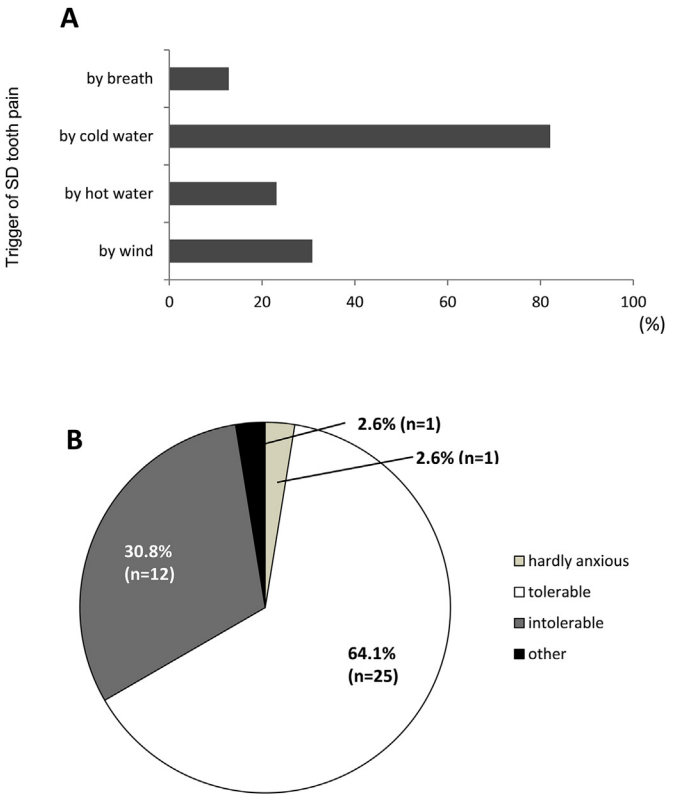

Fig. 4. Features of steroid-derived tooth pain. **(A)** Triggers of steroid-derived tooth pain. Numbers of patients experiencing pain in response to each trigger are shown. **(B)** General pain severity. The pain was tolerable in most cases.

Table 3
Summary of differences in the manifestations of SD tooth pain and true DH pain.

	SD tooth pain	DH pain
Duration	Continuous	Transient
Intensity	Severe	Not severe
Thermal trigger	Both cold and hot stimulation	Usually cold stimulation
Causal teeth number	Multiple	One or a few
Root exposure	Not related	Causally related
Standard DH treatment	Temporarily effective	Effective
Reduction/discontinuation of the steroid	Effective to diminish/resolve	Not effective

SD, steroid-derived; DH, dentin hypersensitivity.

quite different from DH, although the symptoms are similar. The mechanisms underlying SD tooth pain remain to be determined, but may be caused by central (central nervous system neurons) and/or peripheral (tooth pulp) systems. Some studies have suggested a relationship between steroid use and histological reactions in the brain, as steroids can cross the blood–brain barrier (8) and the brain expresses steroid receptors (9,10). In addition, steroid administration induces degeneration and cell death in neurons (11–13). However, these reports showed no evidence to explain the origin of SD tooth pain. We recently reported that, following steroid administration, particular glial cells are activated in the subnucleus caudalis of the trigeminal sensory complex of rats, where trigeminal primary afferent fibres innervating orofacial areas project (4). Our findings may indirectly show the possible relationship between steroid administration and trigeminal nociception. At present, we cannot completely explain why external stimuli (cold water, hot water, and wind) evoke only tooth pain after steroid

administration without affecting other oral tissues, as the trigeminal primary afferent fibres from the subnucleus caudalis innervate not only the dental pulp but also other oral tissues. Consequently, we consider that a peripheral (afferent nerve fibre) mechanism, rather than a central one, likely underlies SD tooth pain.

Regarding the peripheral effect of steroid administration, it has been reported that steroids inhibit dentin formation in a dose-dependent manner in prenatal rats (14); however, there is no published evidence that steroids induce morphological changes in the tooth pulp. Physiological evidence of the hydrodynamic theory (15), which is the main proposed mechanism of DH pain, suggests that pain sensation is induced by fluid movement within the dentinal tubules in response to mechanical, osmotic, or evaporative stimuli. This could also be a potent peripheral mechanism underlying SD tooth pain. The dental pulp, surrounded by rigid dentin walls, has much lower interstitial compliance for the pulp tissue to extend or shrink (16) compared with other tissues such as skin and muscle, which have relatively high compliance (17,18). Because the mineralocorticoid activity of prednisolone and/or methylprednisolone is reported to induce peripheral oedema in the skin (19), if this influences pulp tissue, then induced oedema could facilitate fluid movement within the dentinal tubules in response to external stimuli. Indeed, it is suggested that hypersensitivity to thermal changes in pulp hyperaemia is strongly related to oedema caused by plasma extravasation (20). Thus, we hypothesise that excessive tissue pressure exerted by pulpal oedema after steroid administration could contribute to the mechanisms underlying SD tooth pain. Moreover, SD tooth pain was not transient, but continuous and severe compared with general DH pain. One possibility is that sensory neuropeptides, such as calcitonin gene-related peptide or substance P, and/or vasodilatation evoked thereof may relate to the onset of SD tooth pain. In this respect, we previously demonstrated that vasodilator responses elicited by noxious stimulation via antidromic activation of nociceptive nerve fibres occurred in the dental pulp (axon reflex vasodilation), suggesting that the spread of neurogenic inflammation was feasible in the dental pulp with rich nerve fibres (21). Unfortunately, SD tooth pain could not be relieved by treatment generally performed for DH, presumably because the excessive oedema-induced tissue pressure in the dental pulp could not be reduced by such dental treatment.

Thus, we demonstrated the possible relationship between steroid therapy and DH-like tooth pain. However, our data could not show the results from a long-term follow-up because of the cross-sectional nature of this study. Therefore, we could not reveal the detailed transition of pain in each patient. Further study is needed to clarify this DH-like tooth pain and delineate the mechanisms by which this pain occurs.

5. Conclusions

We have validated anecdotal information that suggests characteristic tooth pain occurs as a side effect of steroid therapy. Such pain bears similarity to DH (e.g., reversibility and occurrence in the absence of inflammation), but is distinguished by the continuous and severe nature of the pain and its induction by hot water simultaneously in multiple vital teeth without obvious root exposure. In addition, this pain was diminished or resolved with reduction or discontinuation of steroid therapy. These findings are significant for clinicians prescribing steroid agents and require further investigation to clarify the mechanisms by which steroids induce such pain and the proper treatment strategy without necessitating discontinuation of steroid treatment.

Conflict of interest statement

The authors have no conflicts of interest to declare regarding the conduct or publication of this research.

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